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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,279	02/03/2005	Charles Richard Jones	JANM-0725/JAB1709USPCT	3868

45511 7590 10/18/2007

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EXAMINER	
HOUGHTLING, RICHARD A	
ART UNIT	**PAPER NUMBER**
4133	

NOTIFICATION DATE	DELIVERY MODE
10/18/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,279	JONES ET AL.	
	Examiner	Art Unit	
	Richard A. Houghtling, Ph.D.	4133	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03 February 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are pending in this application, and claims 8-11 were cancelled by applicant in a preliminary amendment filed on February 3, 2005, thus claims 1-7 and 12-15 are examined on there merits, herein.

Priority

2. Applicants' claim to foreign priority to EP 02255676.5 is acknowledged and entered in the record.

Information Disclosure Statements

3. Receipt of an information disclosure statement filed by applicants on February 3, 2005 is acknowledged; examiner entered the disclosure into the record and references were considered.

Claim Objections

4. Claim 12 is objected to because of the following informalities: the claim appears to be incomplete, as it appears to be missing a word as well as a period. Appropriate correction is required.

5. Claim 4 is objected to because of the following informalities: the alpha-adrenoceptor antagonist abanoquil is listed twice; first occurrence (line 2) and second occurrence (line 3). Appropriate correction is required.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 12-15 are rejected under 35 U.S.C. 103(a) as being obvious over Wyllie (US Patent 7,138,405) and Sanger et al. (US Patent Application 2002/0128172).

The applied reference (Wyllie, '405) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be

overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Applicants' invention is drawn to a combination of two antagonists—an alpha-adrenergic receptor antagonist and a serotonergic receptor subtype-4 (5-HT_4) antagonist for pharmacological use in the treatment of lower urinary tract symptoms (LUTS). Applicants' claims are drawn to: a pharmaceutical composition (claims 1-7), a product containing the two medicaments (claim 12) and a method for treatment (claims 13-15).

Applicants' pharmaceutical composition (claim 1) comprises a 5-HT_4 antagonist and an alpha-adrenergic antagonist. The alpha-adrenergic receptor antagonists may be either non-selective for the $alpha_1$-subtype or $alpha_2$-subtype of receptors (claim 2) or selective for the $alpha_1$-subtype (claim 3); and finally, a list of candidate alpha-adrenergic antagonists are provided, as follows: abanoquil, alfuzosin, indoramin, tamsulosin, doxazosin, parvosin, terazosin, abanoquil, prazosin and pharmaceutically acceptable salts thereof (claim 4).

Claims 5-7 of applicants' invention further limits the composition of claim 1, by defining the 5-HT_4-receptor antagonist. A selective antagonist is required by claim 5, which is to be selected from the following list: SB 205800, SB 203186, R50595, GR113808, GR138897, LY-353433, DAU 6285, SDZ 205-557,

RS 23597-190 or (3S-trans)-4-(4-[[(8-chloro-3,4-dihydro-2H-benzo[b][1,4]dioxepine-6-carbonyl)-amino]methyl]-3-hydroxy-piperidin-1yl)-butyric acid) and their pharmaceutically acceptable salts thereof (claim 6), which is further limited to (3S-trans)-4-(4-[[(8-chloro-3,4-dihydro-2H-benzo[b][1,4]dioxepine-6-carbonyl)-amino]methyl]-3-hydroxy-piperidin-1yl)-butyric acid) and its pharmaceutically acceptable salts thereof (claim 7).

Claim 12 is drawn to a product comprising a first pharmaceutically acceptable composition of an alpha-adrenergic antagonist and a second pharmaceutically acceptable composition of a 5-HT_4-receptor antagonist for use as a combined preparation for simultaneous or sequential use.

Finally, claims 13-15 are drawn to methods for the treatment of LUTS (claim 13) or specific symptoms such as overactive bladder (claim 14) or benign prostate hyperplasia (claim 15). The methods of claims 13-14 are each administered to a host in need thereof; whereas, claim 15 is administered to a mammal in need thereof. In each of the methods, the active step comprises administering an effective amount of an alpha-adrenergic antagonist in combination with a 5-HT_4-receptor antagonist.

Wyllie ('405) teaches a method and a pharmaceutical composition for treating lower urinary tract symptoms, which is associated with benign prostatic hyperplasia by using a combination of two antagonists—an alpha-adrenergic

receptor antagonist and a muscarinic-subtype acetylcholine receptor antagonist (see abstract). Similar to applicants' claimed invention (claims 1-3), Wyllie ('405) teaches that the alpha-adrenergic antagonist may be a selective $alpha_1$-receptor antagonist (col. 3, lines 45-46) or a nonselective $alpha_1$- or $alpha_2$-adrenergic receptor antagonist (col. 3., lines 46-47). Also taught is a list of possible alpha-adrenergic antagonists (see col. 3, lines 52-67 and col. 4, lines 1-3) that includes each drug mentioned by applicants' claim 4 except for parvosin.

Wyllie ('405) thoroughly teaches a combination of the alpha-adrenergic receptor antagonist and the muscarinic antagonist as shown in the more than 5 examples provided in columns 9 and 10. In addition, Wyllie also claims a method for treating the lower urinary tract symptoms associated with BPH in mammals comprising administering to a mammal suffering from BPH an effective amount of an alpha-adrenergic receptor antagonist selected from a large list (and its pharmaceutically acceptable salts thereof) in combination with a muscarinic antagonist also selected from a list that also includes pharmaceutically acceptable salts thereof.

Similar to applicants' product in claim 12, Wyllie ('405) also teaches similar techniques and products for administering the antagonists (see col. 5, lines 36-67 and col. 6, lines 1-26). Specifcally, the method of Wyllie ('405) described by claims 1-3 also teach that the antagonists may be administered as simultaneous, separate or sequential drug treatments. Wyllie ('405) however, does not teach,

the specific combination of an alpha-adrenergic receptor antagonist and a $5HT_4$ receptor antagonist.

Sanger et al. teaches that urinary bladder hypersensitivity may be treated by administration of $5HT_4$-receptor antagonists (see abstract and ¶ 6 in its entirety). Sanger et al. further teaches specific examples of $5HT_4$-receptor antagonists (see ¶ 9-10) that are "believed to be associated with conditions involving inter alia the urinary tract (e.g., urinary incontinence)," (¶ 10, lines 3-5). Administration of the $5HT_4$-receptor antagonist (or a pharmaceutically acceptable salt) is also taught (see ¶ 26-27). However, Sanger et al. does not teach the combination of the $5HT_4$ receptor antagonist with the alpha-adrenergic receptor antagonist.

Both compositions and methods taught by Wyllie ('405) and Sanger et al. are directed toward pharmaceutical compositions and methods of administration for the treatment of lower urinary tract symptoms. As taught by Wyllie ('405) a frequent occurrence in BPH is an increase in urgency and frequency of urination. Likewise, Sanger et al. teaches that bladder hypersensitivity can result in urinary incontinence (also termed, an overactive bladder). Furthermore, from a pharmacological perspective, it is well known within the art that muscarinic receptor antagonists often result in the presence of unpleasant side effects (i.e., dry mouth, dry eyes or headache) that may reduce patient compliance. Therefore to increase patient compliance and reduce the possible unwanted side

effects, substitution of the $5HT_4$-receptor antagonist for the muscarinic antagonist would have been obvious to do and likely profitable. Finally, it is *prima facie* obvious to combine these two teachings with the result being that of the composition and/or method of applicants' claims 1-7 and 12-15. The basis for this *prima facie* obviousness rejection can be found in the following case law:

"It is however, *prima facie* obvious to combine two compositions taught in the prior art useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069,1072 (CCPA 1980).

Conclusion

In conclusion, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard A. Houghtling, Ph.D. whose telephone number is 571-272-9334. The examiner can normally be reached Monday to Thursday from 8:00 am - 5:00 pm. The examiner can also be reached on alternate Fridays (9 am – Noon).

The Group 1600 fax phone number where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on 571-272-0911.

Richard A. Houghtling, Ph.D.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

10/14/07